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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,363	07/01/2003	John R. Desjarlais	A-71486-2	4995

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Robin M. Silva
DORSEY & WHITNEY LLP
Suite 3400
Four Embarcadero Center
San Francisco, CA 94111-4187

EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/611,363	DESJARLAIS ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *2,4,12,14,17,19,22,24,27,28,31 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-11,13,15,16,18,20,21,23,25,26,29,30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/04,6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

Applicant's election without traverse of Group I (claims 1-32) and election of modifications at positions 223, 225, 226, 237 and 269 in the reply filed 05 July 2006 is acknowledged. In addition, all other claims reciting elected modifications (and combinations of those elected modifications) will be considered.

Claims 2, 4, 12, 14, 17, 19, 22, 24, 27, 28, 31 and 33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group (or elected modification), there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 17 April 2006.

Claims 1, 3, 5-11, 13, 15, 16, 18, 20, 21, 23, 25, 26, 29, 30 and 32 are under examination.

Inventorship

In view of the papers filed 16 April 2004, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by the addition of Shannon A. Marshall.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 16 August 2004 and 30 June 2006 were received and comply with the provisions of 37 CFR §§1.97 and 1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits.

Sequence Rules

The specification is not in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations. When the description of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier (SEQ ID NO:), in the text and claims of the patent application.

37 CFR 1.821(a) presents a definition for nucleotide and/or amino acid sequences. This definition sets forth limits in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Please see MPEP section 2422.01.

The specification refers to sequences in Figure 2A, but does not identify the sequences by their sequence identifiers. Sequences appearing in drawings should be referenced in the corresponding Brief Description thereof. See 37 C.F.R. §1.58(a) and §1.83. Appropriate correction is required.

Applicant must submit a response to this Office Action and compliance with the sequence rules within the statutory period set for response to this Office Action.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-11, 13, 15, 16, 18, 20, 21, 23, 25, 26, 29, 30 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a variant RANKL protein wherein said variant RANKL comprises modifications at positions R223M, R223E, R223Q, H225T, H225N, H225E, H225R, E226Q, E226D, E226R, Q237T, Q237K, Q237E, E269R, E269T, E269Q and E269K *in combination with mutation C221S/I247E,*

does not reasonably provide enablement for:

a variant RANKL protein wherein said variant RANKL comprises modifications at positions R223, H225, E226, Q237, E269.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant specification teaches that normal bone remodeling is a process in which new bone deposition by osteoblast is balanced through bone resorption by osteoclast. RANK is activated by the binding of its ligand, RANKL, which leads to differentiation, survival and fusion of pre-osteoclasts to form active bone resorbing osteoclast (page 1). The specification teaches that the present invention is directed at generating novel variants of human RANKL protein, comprising the extracellular domains of RANKL, which behave as RANKL antagonists or superagonists and modifications that confer soluble expression in E. coli.

The specification states that it has been observed that human RANKL forms inclusion bodies when expressed in E. coli. Soluble expression allows for efficient and cost-effective production and manufacturing of human RANKL variants (page 3, line 25-page 4, line 5). Thus, it is important that variant RANKL proteins are soluble. The specification teaches that only specific RANKL variants (C221S/I247A, C221S/I247D, C221S/I247K, C221S/I247Q and C221S/I247E) showed soluble expression in bacteria (page 39, Table 1). The specification teaches the construction of a RANKL variant library, comprising the solubility-imparting modification C221/I247E. The specification teaches the classification of RANKL variants. Specific RANKL variants exhibited non-

agonistic activity (i.e. inhibition of osteoclastogenesis with or without RANK receptor binding and/or inhibition of OPG binding)(Table 2 and pages 44-47).

It is known to those skilled in the art that certain positions in a sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo *et al.,* 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 433-440 and 492-495). For instance, a point mutation change from glutamine to aspartic acid at position 226 enables a variant RANKL protein to go from non-binding to binding of RANK receptor. A point mutation change from glutamine to threonine at position 269 still enables a variant RANKL protein to bind RANK receptor but inhibits the variant from binding OPG. It would be apparent to one skill in the art, that the effects of these types of changes are largely unpredictable as to which ones have a significant effect versus not. The instant specification teaches specific variant RANKL proteins, which are suitable. Therefore, the recitation of any RANKL variant protein results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement.

Lastly, claim 32 recites, "a pharmaceutical composition comprising a variant RANKL protein according to claim 1 and a pharmaceutical carrier" and thus reads on

use of that composition for treatment/therapy. The specification fails to disclose a direct correlation (working examples, animal models, etc.) between the use of the instant invention and a method for treatment in subjects. Specific RANKL variants were able to inhibit osteoclastogenesis *in vitro.* This activity is not predictive of the activity RANKL variants might have *in vivo.* Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo.* These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo.* Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light. Thus, it could not be predicted that the cell culture data presented in the specification would be in any way correlative with therapeutic agents for *in vivo* treatments.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity and the large quantity of experimentation necessary to show a correlation between a pharmaceutical composition comprising a RANKL variant and treatment of a specific disease/condition (including amounts and routes of administration for treatment in mammals), the absence of working examples directed to same, the complex nature of the invention, the state of

the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5-11, 13, 15, 16, 18, 20, 21, 23, 25, 26, 29, 30 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims are indefinite in the recitation of amino acid positions in the absence of a referenced SEQ ID NO:. It is not clear what sequence is intended by the claims and thus the metes and bounds of the claims cannot be determined by one skilled in the art.

Claim Objections

Claim 3 is objected to because of the following informalities: The word "substitution" is misspelled. Appropriate correction is required.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
9/13/06

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER

AU 1647

9/18/2006